VOLUME XII March 1956 NUMBER 3

Clinical Proceedings

OF THE

CHILDREN'S HOSPITAL

ASHINGTON, D. C.

to help you combat iron deficiency in infants...

How Fer-In-Sol improved infants' blood pictures

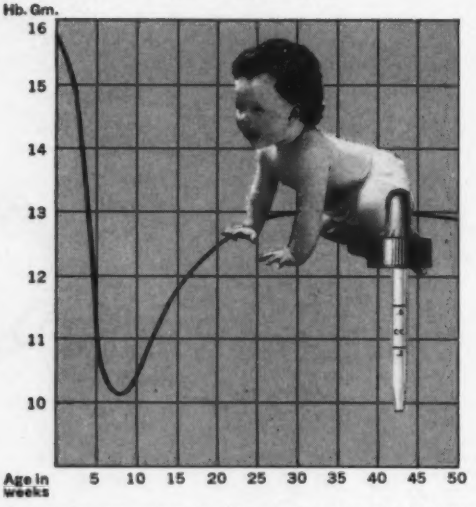


Chart adapted from Niccum, Jackson and Stearns: A.M.A. Am. J. Dis. Child. 88: 553, 1954.

Mean hemoglobin determinations of infants on a predominantly milk diet receiving Fer-In-Sol. The Fer-In-Sol dose was 5 mg. of iron (0.2 cc.) per day at 3 months, increased to 10 mg. of iron (0.4 cc.) after 6 months of age.[1]

Fer-In-Sol

iron in a drop for infants and children

"Iron deficiency anemia has a peak incidence between six months and two and one-half years..."

Smith and Rosello[3] found that the peak incidence of iron deficiency in infants and children occurred between the ages of 6 and 24 months, when growth is most rapid. Sturgeon[4] reports that published data indicate iron deficiency in infants is common. Although consuming normal diets, the majority of infants in the last half of the first year of life, and throughout the second year of life, "exist in relatively severe states of iron deficiency (30% or more depleted)."[4]

Niccum, Jackson and Stearns[1] found that prophylactic administration of Fer-In-Sol in small daily doses "was sufficient to maintain hemoglobin values at a constant level throughout the latter half of infancy in all full term infants"... resulted in significantly higher hemoglobin values than did ferric ammonium citrate ... did not produce gastrointestinal disturbances.

FER-IN-SOL

Fer-In-Sol® provides a pleasant way to supply ferrous sulfate—a well tolerated, well absorbed and efficiently utilized form of iron. The vehicle is acidulous to improve absorption and utilization. The good taste of the solution makes it readily acceptable to young children. And tolerance is good.

Only 0.3 cc. of Fer-In-Sol supplies 7.5 mg. of iron—more than the Recommended Daily Allowance for children up to 4 years old. Fer-In-Sol is supplied in 15 cc. and economical 50 cc. bottles, with the new calibrated 'Safti-Dropper' of unbreakable plastic.

(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 88: 553, 1954. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

MEAD

SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

MEAD JOHNSON & COMPANY, Suite 419 Eig Building, 8641 Colesville Road, Silver Spring, Maryland. JUniper 9-1222

CLINICAL PROCEEDINGS
OF THE CHILDREN'S HOSPITAL
2125 13th Street, N.W., Washington 9, D. C.

PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinicopathological conferences and from the monthly Staff meeting.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D. C. Please notify on change of address.

Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

AGAMMAGLOBULINEMIA

Subject Outline and Case Report*

J. William Oberman, M. D.

Agammaglobulinemia is a disease syndrome characterized by:

1. Recurrent and severe bacterial infections.
2. Marked reduction or absence of both serum and extravascular gamma globulin (more exactly described as a total lack of immuno-globulins since the antibody portion of the beta$_2$ globulin is absent as well as the gamma globulin).
3. Absence of naturally occurring and other circulating antibodies.
4. Inability to produce antibodies to potent bacterial, viral, or rickettsial antigens.

There are two types:

Congenital: Extreme susceptibility to infection in children beginning after the loss of passively transferred maternal gamma globulin (usually beginning sometime after the first six months of life). This is usually a true agammaglobulinemia, and is postulated to be an inherited, recessive, sex-linked mendelian characteristic so far reported only in boys.

Acquired: The same syndrome occurring in adults of both sexes. This type usually does not start until the "teens" or early twenties and may begin even later. This type is usually an extreme *hypo*gammaglobulinemia.

Other diseases with hypogammaglobulemia are usually associated with reduction of total proteins, especially the albumin fraction. The most common complaint is *edema* due to the low serum albumin, but all are also susceptible to infection due to associated low gamma globulin. These would include the following:

1. nephrotic syndrome
2. malnutrition
3. hepatic insufficiency
4. leukemia
5. malignant lymphomas
6. familial idiopathic dysproteinemia
7. transient depression following infection
8. multiple myeloma (may be low or high but in either event there is an increased susceptibility to infection).

The following case report exemplifies the congenital type of hypogammaglobulinemia in a boy from a family with an unusual history of susceptibility to infections.

* From the Research Foundation of Children's Hospital. This study was supported by a grant from the National Institutes of Health.

CASE REPORT

R. S., a 9½ year old white boy, was first seen in Children's Hospital Out Patient department in 1948 at the age of 2 years, where he was treated for an episode of bronchitis and tonsillopharyngitis. At that time, his parents gave the past history of "measles" at age 1 year, a "boil" at age 1½ years, and bilateral conjunctivitis at age 1½ years. Since that time he has been hospitalized a total of 15 times with the following complaints:

1/ 8/49 cellulitis of the leg
1/20/49 bronchitis and tonsillopharyngitis
6/18/49 septicemia with possible osteomyelitis of the hip
12/ 9/49 septicemia with cellulitis of the leg and bronchitis
1/ 6/50 chickenpox with bronchopneumonia
1/11/50 measles with bronchopneumonia
9/ 5/50 bilateral bronchopneumonia
12/27/50 bilateral bronchopneumonia
2/15/51 arthropathy of unexplained origin; possible rheumatoid arthritis
4/25/51 otitis media, pharyngitis, bronchitis
12/27/51 pneumonia, left base
12/30/52 bilateral bronchopneumonia
3/22/54 convulsive disorder
10/30/54 bilateral bronchopneumonia
11/14/54 bilateral bronchopneumonia, unresolved.

In recent years, the patient has seldom been without pulmonary complaints. He has a more or less constant deep cough, productive of varying amounts of yellowish sputum.

Because of numerous infections a diagnosis of agammaglobulinemia was first suspected during the 1952 hospital admission, and an intensive investigation was undertaken at that time.

Past history revealed a completely uncomplicated pregnancy and delivery. His neonatal condition was excellent. Early neuromuscular development was normal. His diet had always been adequate. He received his routine DPT immunizations at three years of age and repeated tuberculin tests had been negative. His previous disease history was as mentioned above.

Family history revealed both parents to be in their forties and in good health. The mother gave a history of two "lung infections" in the past but has otherwise seldom been ill. There was no history of familial disease on either side of the family. The patient was the eighth of ten children. Of seven children older than he, four died between the ages of one and three years, one of pneumonia, one of multiple furunculosis and pneumonia, another of empyema secondary to pneumonia, and the fourth from "lung infection". Three remaining older children were in good health. Of two younger children, one was in good health and another had died at the age of 18 months from a medulloblastoma. (Since the above investigation, the mother has had another child who remains in good health).

Intensive study and review of past admissions during this hospitalization revealed: repeated blood studies were normal except for evidence of bacterial infection; repeated urinalyses were normal; eosinophil counts ranged from 0 to 590; bleeding and clotting times were normal, and bone marrow examination showed evidence of a reaction to infection with a shift to the left. Blood chemistries including blood bilirubin, blood urea nitrogen, total protein and albumin to globulin ratio, thymol turbidity and cephalin flocculation, bromsulphalein, serum cholesterol, fasting blood

sugar, prothombin time, blood fibrinogen level, and cold agglutinins were all normal. Spinal fluid examination was normal. Cultures on multiple occasions of urine, gastric fluid, stool and nasopharyngeal secretions for bacteria, acid fast bacilli or fungi were either negative or were non-contributory. Duodenal drainage on three occasions revealed normal activity for trypsin, lipase, and amylase. Complement fixation test for trichinella was negative.

Examination of the stool revealed a severe infestation with *Giardia lamblia*. This was adequately treated with atabrine and cleared without any improvement in the patient's general condition. Numerous X-ray films of the chest revealed evidence of pneumonia. Bronchograms performed on two occasions did not reveal evidence of bronchiectasis. Sinus X-rays showed evidence of chronic maxillary sinusitis. A gastro-intestinal series was non-contributory. A Kunkel test for gamma globulin on two occasions revealed values of 0.6 gm. and 0.52 gm. of this substance. Serum electrophoresis, however, indicated that there were negligible quantities of gamma globulin present in this patient's serum.

The diagnosis of hypogammaglobulinemia having been established, the boy was treated with 3.2 gms. (20 cc) of gamma globulin monthly. There was a marked improvement in his condition. He was completely free from infection with the exception of one occasion when his mother failed to bring him in for his gamma globulin injection; at that time there again developed bilateral bronchopneumonia, necessitating hospitalization. He has been taking sulfadiazine in a dosage of 0.5 gm./day. In March of 1954 he had a grand mal convulsion. Examination at that time revealed a mentally retarded child with a diffusely abnormal EEG and he was placed on dilantin therapy with good clinical response.

From July through November 1955, he received no gamma globulin injections in an attempt to discover whether he was now capable of forming any gamma globulin of his own. When seen in November 1955 he was found to have pneumonia again. The serum gamma globulin level at this time was 77 milligrams per 100 ml. This illness responded promptly to penicillin and gamma globulin therapy. Because of a constant expectoration of yellowish sputum even when there is no evidence of concurrent infection, he is to be admitted to the hospital in the near future for further investigation of the presence of bronchiectasis.

DISCUSSION

Physiology Of Gamma Globulin

Gamma globulin normally comprises about 13–20 per cent of the total serum proteins and consists chiefly of immunoproteins together with a considerable quantity of non-specific gamma globulin of unknown significance. Beta$_2$ globulin fraction also contains antibodies, specifically blood group isohemagglutinins, typhoid "O" agglutinins and true Wasserman reagin. The normal adult has about 25 grams of circulating gamma globulin plus 25 grams of tissue gamma globulin in dynamic equilibrium.

The level of gamma globulin is higher in the newborn than in the pregnant mother at term, falls sharply to reach a low point at about 2–3 months of age, and then rises slowly as the child contracts various diseases to reach the adult level at sometime between 2–6 years of age.

The half-life of injected I^{131} labelled gamma globulin in adults is 13.1 plus or minus 2.8 days and in children 20.3 plus or minus 4.1 days.

Clinical Hypogammaglobulinemia

A. *Frequently occurring severe bacterial infections:* pyoderma, purulent conjunctivitis, otitis media, purulent sinusitis, acute hepatitis, pneumonia, pyelonephritis, meningitis, septic arthritis, and enterocolitis. Septicemia is frequently present. In adults, after repeated episodes of infection, bronchiectasis, chronic hepatitis and sprue-like syndromes occur.

B. *Bacteria:* usually pneumococci, staphylococci, meningococci and *H. influenzae*. In adults *H. influenzae* infections are common (these infections are usually rare in adults without agammaglobulinemia).

C. *Viral infections:* may be repeated episodes of chicken pox, measles, mumps and poliomyelitis. Patients are able to handle viral infections normally and usually do not become seriously ill with them. However, no detectable antiviral antibodies are found in the serum after these infections.

Laboratory findings

A. *Serum proteins:*

Total may be within the normal range or somewhat reduced. The A/G ratio is increased. Serum normally contains 600–1200 mg. of gamma globulin per 100 cc. In congenital agammaglobulinemia the value is usually less than 30 mg. per 100 ml. and in the acquired type, less than 100 mg. per 100 ml. The usual response of a *normal* person to infection is a rise in gamma globulin.

B. *Immunology:*

1. Absence of common circulating antibodies: Forsman antibody, cold agglutinins, anti-streptolysin "O" titer, complement fixation or virus neutralizing antibodies. The absence of isohemagglutinins against heterologous blood group cells indicates a deficiency in $beta_2$ globulins.

2. Inability to induce antibody production to potent bacterial, viral or rickettsial antigens: typhoid, paratyphoid, pneumococcal polysaccharide, DPT, influenza, mumps, Rocky Mountain spotted fever, Q fever, and typhus. The Dick & Shick tests remain positive; the tuberculin test remains negative. Vaccination usually takes and may result in the vaccinia, vaccinoid or immune type of reaction. The reason for this is unknown; it probably indicates a different unknown type of immune mechanism. *Vaccinia gangrenosum* occurs rarely and for this reason some investigators believe vaccination is contra-indicated in these patients.

3. Successful homotransplantation of skin: this is always unsuccessful in normal persons (except identical twins) because of antibody formation by the recipient with slough of the graft.

C. *Other laboratory tests:*

1. Normal liver function tests when abnormal tests would be expected (as in hepatitis): cephalin flocculation, thymol turbidity.

2. Kunkel gamma globulin is low (0–1 unit; normal 5–13 units).

3. Unaffected tests: serum complement is normal. The sedimentation rate increases in the presence of infection (plasma contains a normal amount of fibrinogen). C-reactive protein and the serum mucoproteins may be positive.

4. Hematological changes: inconstant

Leukocytosis or persistent, transient, or cyclic neutropenia, lymphocytosis or lymphopenia, eosinophilia, normal eosinophils or eosinopenia.

Pathology

A. Bone marrow, lymph node and splenic biopsy: there is a universal lack or marked deficiency of plasma cells in these centers and the reticulum is especially prominent. Following antigenic stimulation (e.g. typhoid antigen) there is an absence of the normally occurring increase in plasma cells in these centers; this indicates diminished lymphopoiesis.

B. Liver biopsy: normal unless evidence of hepatitis or cirrhosis is present.

Pathologic Physiology

The basic defect is apparently due to a failure of synthesis of gamma globulin (immunoglobulins) and not a function of abnormal metabolism of proteins in general nor of an increased destruction of gamma globulins. The half life of injected gamma globulin in patients with agammaglobulinemia ranges from 20 to 30 days, values greater than that of normal adults and within the normal range in children. This excludes rapid catabolism of gamma globulin and probably means that the relative amount utilized per unit of time decreases as the level falls.

Is the basic defect an abnormality of reticular formation? Tissue lymphocytes may give rise to blood lymphocytes or undergo cytolysis giving rise to blood antibodies (the latter reaction is dependent on the level of blood corticoids). However, either lymphopenia or lymphocytosis may be present and the lymphoid tissue has been normal in some instances.

Even with intensive ACTH therapy, there is no increase in gamma globulin; neither a relative excess or deficiency of 17-hydroxycorticosteroids seems to provoke or relieve agammaglobulinemia.

Therapy

A. Antibiotics for acute infection: prophylactic antibiotics may be dangerous due to change in the bacterial flora.

B. Gamma globulin 0.1 gm/kg. intramuscularly every 2–4 weeks. Normal levels of gamma globulin are neither necessary nor practical; 100–150 mg. per 100 ml. are adequate. Intravenous administration will give severe hypotensive reactions and no more than 20 ml. intramuscularly should be given. Large amounts may cause chills, fever, myalgia and faintness.

Hypergammaglobulinemia

In some asymptomatic members of the family of patients with agammaglobulinemia, a hypergammaglobulinemia has been present. This may be a qualitative disturbance in gamma globulin production. Is this a heterozygous recessive character with agammaglobulinemia being a homozygote?

Another group of children have demonstrated hepatomegaly, splenomegaly, generalized lymphadenopathy and markedly elevated serum gamma globulin (1.0–4.5 gm. per 100 cc.). These children also have recurrent or chronic skin and respiratory infections. Biopsies and autopsies in these children show a diffuse mononuclear reaction with infiltration of plasma cells in all organs. This is exactly the opposite from agammaglobulinemia. Is this a *dys*gammaglobulinemia and are the pathological findings the cause or the effect? These questions remain unanswered.

BIBLIOGRAPHY

1. Good, R. A.: "Agammaglobulinemia", *Bull. Univ. Minnesota Hosp.*, **26:** 1 (1954).
2. Young, I., Wolfson, W., and Cohn, C.: "Studies in Serum Proteins", *Am. Jour. Med.*, **19:** 222 (1955).
3. Gocke, T., Porfido, F. and Gallagher, E.: "Agammaglobulinemia", Grand Rounds of Medical Dept. of Georgetown Univ. School of Med., March 22, 1955.
4. Janeway, C., Craig, J., et al.: "Hypergammaglobulinemia Associated with Severe Recurrent and Chronic Nonspecific Infection", *Am. J. Dis. Child.*, **88:** 388 (1954).

SUSCEPTIBILITY TO INFECTION AFTER SPLENECTOMY PERFORMED IN CHILDHOOD*

Richard Hoefnagel, M.D.†

In their article, "Susceptibility To Infections After Splenectomy Performed In Infancy", King and Shumacker [1] report on severe infections following splenectomy in five infants under the age of six months. In all these infants splenectomy was performed because of congenital hemolytic

* See editorial this issue.

† Present address: Children's Hospital, Boston, Massachusetts.

anemia. In four of the five infants, either meningitis or overwhelming meningococcemia developed from six weeks to three years after operation, and one of the four died of the infection. The fifth child was returned to the hospital a few days after discharge following splenectomy with a rapidly fatal febrile illness, suggestively infectious in nature. The authors, in the course of their discussion, make the following comment: "Why serious infection apparently tends to follow splenectomy performed in infancy and not in patients whose spleens are removed at an older age is certainly far from clear". The following two cases are reported because they tend to confirm the observation that splenectomy performed in a young child may increase susceptibility to severe infections.

CASE I

G. E. J. was born in 1946 after an uneventful pregnancy and an uncomplicated delivery. The birth weight was 6 pounds, 4 ounces. He was circumcised on the sixth day of life, and bled profusely after the circumcision. Growth and development were essentially normal. At two months of age infantile eczema occurred and was treated with hypoallergenic formulas and ointments. The eczema was cured at the age of one year and a half. Between the age of one and four years the child had numerous minor infections, e.g., paronychia, otitis media, conjunctivitis and bronchitis. The patient was allergic to walnuts, which produced hives. At approximately eight months of life, easy bruising was noticed which persisted until after splenectomy later in life. Also in his eighth month the patient bled severely from his mouth, and in the course of his life had several severe nosebleeds, some lasting as long as eleven hours. He had no childhood diseases, and had received no immunizations or vaccinations.

Family history: The father, who is 42 years old, is living and well. He had several severe nosebleeds between the ages of five and eight years. There is a questionable history of hay fever and bronchial asthma in his younger years.

The mother is 33 years old, living and well, with an essentially normal past history. There are siblings; 1. N. E. J., boy, aged 16 years is living and well. 2. M. J., girl, aged 15 years, bruised easily up until the age of three years, but not thereafter. The menarche was normal at age 14 years. 3. D. J., boy, aged one year, is apparently normal. There is no knowledge of any familial diseases.

First admission of G. E. J.: (July 27 to August 3, 1951). On admission this well nourished and well developed five year old white boy was found to have bruises covering the entire body. The spleen was not palpable. The child was discharged with the diagnosis of idiopathic thrombocytopenic purpura.

The results of the significant laboratory work done during this hospitalization follow:

Blood: Platelets average, 20,000 per cu mm; circulating eosinophils 1700 per cu mm; bleeding time, 4 minutes; clotting time, osmotic fragility and prothrombin time, normal; clot retraction, 20 per cent in two hours; hemoglobin, 9.5 and 9.0 gm per 100 ml; white blood cells, 7,200 and 6,900 with segmented forms 52 and 41 per cent, bands 2 per cent, lymphocytes 39 and 36 per cent, monocytes 1 and 2 per cent, eosinophils 5 and 20 per cent, and basophils 1 per cent.

Bone marrow examination: Erythroid hyperplasia with an increased number of eosinophils (12 per cent), and numerous megakaryocytes, a few of which are immature.

Following this admission ACTH was given on an out-patient basis for two weeks.

Second hospital admission: (From February 4, to February 16, 1952). Because of the lack of permanent response to the ACTH, the child was readmitted. Skin bruises, and nosebleeds had returned prior to admission and on several occasions gross blood was noted in the urine and stool. A splenectomy was performed on February 7, 1952, at the age of six years, and the child had an uneventful postoperative course. The results of the laboratory work done during this admission follow:

Urinalysis was normal; *Blood:* platelets preoperative, less than 10,000 per cu mm, and postoperative, a rapid rise to a level of 200,000 per cu mm; hemoglobin, white blood cells and differentials, not remarkable except for a 4–10 per cent eosinophilia; bleeding time preoperative, 4 minutes; clot retraction time preoperative, incomplete in 24 hours, and on third postoperative day, complete in 3 hours.

Third hospital admission: (From September 26, to September 27, 1952). The child was admitted eight months post-splenectomy, in apparent acute infectious shock. The patient was well until two or three days prior to admission at which time some fever and restlessness developed. On the day of admission the temperature spiked, he had a chill, and vomited once. On the way to the physician's office, shortly before admission, the boy suddenly became cyanotic and lost consciousness. Upon arrival at the hospital he was an acutely ill, comatose child with a temperature of 107.6°F. rectally; the pulse rate of 160 per minute could only be counted by auscultation; blood pressure was unobtainable; there were severe cyanosis, and gasping respirations. The skin was moist but clear, and the extremities were cold. Shortly after admission purpuric spots appeared on the body, increasing rapidly in both size and number. Despite prompt treatment with intravenous adreno-cortical extract, antibiotics and fluids, the child died six hours after admission. An autopsy was performed.

The results of the laboratory work done on this hospitalization are as follows:

Blood: hemoglobin 16.0 gm per 100 ml; white blood cells 2,300 with 28 per cent segmented forms, 5 per cent bands, 1 per cent young forms, 55 per cent lymphocytes and 11 per cent eosinophils; platelets absent; 3 nucleated red blood cells per 100 white blood cells; spinal fluid, 2 cells per cu mm with normal protein and sugar and no growth on antemortem and post-mortem cultures.

Autopsy summary: Primary pathology consisted of hemorrhagic extravasations into the adrenals, lungs, heart, liver, kidneys, stomach, diaphragm, lymph nodes and skin. The hemorrhage in the adrenals was of sufficient extent to obscure corticomedullary landmarks, and microscopically the cells of the adrenals showed varying degrees of degeneration and dissolution.

In addition to the hemorrhagic phenomena, there was edema of the brain, evidenced by flattening of the gyri and sulci. Microscopically there was evidence of nerve cell degeneration in the brain.

Pathological diagnoses: 1. Waterhouse-Friderichsen Syndrome. 2. Cerebral edema and degeneration.

CASE II

E. L. J., brother of G. E. J., was born in 1948 after an uneventful pregnancy and an uncomplicated delivery. The birth weight was 6 pounds, 11 ounces.

No excessive bleeding occurred after circumcision which was performed on the sixth day. At the age of three years easy bruising of the skin was noticed, and the first severe nosebleed occurred. Nosebleeds recurred at intervals, some of them lasting as long as eight hours. They stopped after splenectomy was performed in 1952, at the age of four years. Growth and development were normal. The child was vac-

cinated in 1952 after splenectomy, and there were no other immunizations. There were no known childhood diseases.

For family history see G. E. J.'s clinical history.

First admission: (From July 27 to August 3, 1951). The patient was admitted after a severe nosebleed, lasting about 8 hours. On admission he was found to be covered with bruises. On this admission, the diagnosis of idiopathic thrombocytopenic purpura was made. The child had repeated nosebleeds during his stay in the hospital. Several transfusions were necessary. After discharge a course of ACTH on an out-patient basis was apparently successful in that it decreased the bleeding tendency and increased the platelets to 135,000/mm³. However, discontinuation of the therapy was followed by a return to the initial state.

The results of the significant laboratory work done on this hospitalization follows:

Blood: platelets average 20,000 per cu mm; circulating eosinophils 750 per cu mm; hemoglobin 7.8 gm per 100 ml; white blood cells 8,900 with 45 per cent segmented forms, 2 per cent bands, 4 per cent monocytes, 6 per cent eosinophils, 1 per cent young forms, 41 per cent lymphocytes and 1 per cent basophils; bleeding time varying between 3 and 10 minutes; clotting time (Lee-White) 4 minutes; prothrombin time normal; clot retraction 10 per cent in 4 hours.

Bone marrow examination: Early erythroid hyperplasia with 9.5 per cent eosinophils and megakaryocytes slightly reduced in number.

Second admission: (From February 4 to February 16, 1952). A splenectomy was performed on February 7, 1952 (patient's brother underwent splenectomy on that same day) with a persisting increase of platelets. A mild infection of the upper respiratory tract complicated the postoperative course, which in other respects was uneventful. Results of significant laboratory work done during this hospitalization are as follows:

Blood: platelets pre-operative between 10,000–30,000 per cu mm with a rapid postoperative rise to a persistent normal level; hemoglobins, white blood counts and differentials not remarkable; bleeding time pre-operative, 4 minutes, 20 seconds; clotting time (Lee-White) pre-operative 18 minutes; clot retraction time pre-operative no retraction in 24 hours and on the third post-operative day retraction complete in two hours.

Third admission: (From September 26 to October 8, 1952). This admission took place eight months post-splenectomy. The brother of the child was admitted on this same day. There was an onset of fever and anorexia three days prior to admission. The fever did not respond to antibiotics. There was no vomiting, diarrhea, cough, headache, earache or sore throat. On admission the child was not in acute distress. The temperature was 105° rectally, the pulse was 140 and regular, and blood pressure was 110/70. Skin, lungs, heart, abdomen, ears, nose and throat were essentially normal. There was marked nuchal rigidity and Kernig's and Brudzinski's signs were present. Treatment consisted of intravenous fluids and terramycin and intramuscular penicillin. The patient became afebrile in 36 hours, and had an uneventful recovery.

The results of the laboratory work done during this hospitalization follow:

On admission *Urinalysis:* essentially normal except for some albumin during the febrile episode; *Blood:* hemoglobin 13.1 gm per 100 ml; white blood cells 12,300 with 41 per cent segmented forms, 34 per cent bands, 13 per cent young forms, 5 per cent monocytes and 7 per cent lymphocytes; total circulating eosinophils none, platelets reduced; *Spinal fluid:* cloudy, protein 65 mg per 100 ml; sugar 20 mg per 100 ml; white blood cells 261 per cu mm with 65 per cent neutrophils and 35 per cent lymphocytes. Cultures of the blood, stool, urine and throat showed no growth or normal

G.E.J. Born 1946	July 1951 Diagnosis: Idiopathic Thrombocytopenic Purpura	Feb. 1952 Splenectomy	Sept. 1952 Waterhouse Friderichsen Syndrome Death		
E.L.J. Born 1948	July 1951 Diagnosis: Idiopathic Thrombocytopenic Purpura	Feb. 1952 Splenectomy	Sept. 1952 Streptococcus Meningitis	Feb. 1953 Overwhelming Infection	Nov. 1954 Overwhelming Infection Death
Admission	1.	2.	3.	4.	5.

FIG. 1. Summary of the admissions of the two brothers described in the text

flora, and spinal fluid cultures showed alpha hemolytic streptococci sensitive to all antibiotics tested except streptomycin.

On the sixth day of hospitalization the laboratory work showed: *Blood:* Hemoglobin 12.5 gm per 100 ml; white blood cells, 13,400 with 42 per cent segmented forms, 11 per cent bands, 16 per cent young forms, 23 per cent lymphocytes, 1 per cent monocytes, and 7 per cent eosinophils; platelets 70,000 per cu mm.

Fourth admission: (February 24, to March 18, 1953), age 5 years. Since discharge after his last admission the patient had done well until about 3 A.M., of the day of admission when he was found to be vomiting, first old food and later bile-stained material. He was seen by a physician at 10 A.M., who noticed reddened ear drums and throat. Six hundred thousand units of penicillin were given intramuscularly. A few hours later the patient suddenly became semicomatose with cold hands and feet, cyanotic lips and profuse diaphoresis. Physical examination on admission revealed a critically ill, comatose child with a temperature of 106.6° rectally. Blood pressure was not obtainable, and pulsations could only be felt over the femoral arteries. The heart rate was 160 per minute. There was marked cyanosis of the lips and the nail beds. The respirations were shallow, and the body was covered with a cold sweat. The skin did not show petechiae. There were no meningeal signs. The ocular fundi were clear. Treatment, which was started immediately, consisted of the administration of oxygen by mask, the injection of caffeine-sodium benzoate and the intravenous administration of adreno-cortical extract in large doses. Intravenous fluids including plasma were given. Chloramphenicol and chlortetracycline were given intravenously every four hours. The child responded to verbal stimuli about two hours after admission. The temperature had come down to 103.2°. The patient had a very stormy and dramatic course during his stay in the hospital.

Forty ml. of gamma globulin were given intramuscularly during his illness. The platelet count remained critically low and on the eighth hospital day a course of cortisone, given by mouth, was started. In total the child received 200 mg. of the drug. A dramatic rise of the platelet count was observed.

The management of the fluid and electrolyte balance was difficult. Several whole blood transfusions were necessary. On the eighth day of hospitalization an electrophoretic analysis of the blood proteins was performed.

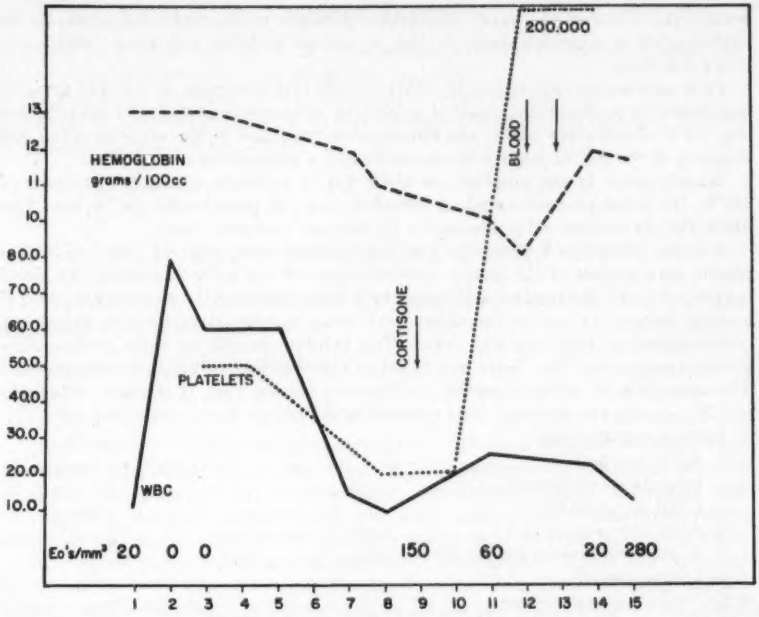


FIG. 2. Summary of the results of hematological data obtained during E. L. J.'s fourth admission.

The results were as follows:

	Relative Per Cent	Grams/100 ml.
Albumin	51.0	3.17
Alpha 1 Globulin	8.7	6.54
Alpha 2 Globulin	8.4	0.53
Beta Globulin	19.5	1.21
Gamma Globulin	12.4	0.77

A/G ratio = 1.04

The normal range of gamma globulin in relative percentage is 11–15 per cent.

Repeated urinalyses were essentially normal except for slight albuminuria during febrile episodes.

Spinal fluid: On admission a clear fluid was obtained containing five white blood cells per cu mm, 24 mg per 100 ml protein and 77 mg per 100 ml sugar. A second lumbar puncture done on the fifth hospital day was traumatic.

Bacteriology: Throat culture, normal flora and beta hemolytic streptococci. Three blood cultures, stool and urine cultures, and two spinal fluid cultures were negative.

Hematology: See graph.

Liver function studies were normal.

After the fourth admission the patient did very well in every respect. He had

several infections of the upper respiratory passages which responded promptly to oxytetracycline administration. A dose of gamma globulin was given empirically every 3 months.

Fifth admission: (November 17, 1954). In the late afternoon of the day prior to admission the patient complained of an earache and some headache. His temperature was 101°F. During the night, the temperature rose, and in the early hours of the morning of the day of admission, the child had a generalized convulsion.

On admission to the hospital the child was in extremis with a temperature of 106°F. No blood pressure could be recorded, and the pulse could not be felt. The child died 50 minutes after admission. An autopsy was performed.

Autopsy summary: A few petechiae were present over the chin. Marked hyperplastic enlargement of the lymph nodes throughout the body was noted. An acute inflammation of the trachea and lungs with focal myocarditis was present. An increased amount of connective tissue with some leukocytic infiltration about the portal spaces of the liver was noted. The kidneys showed an early proliferative glomerulonephritis. The heart and kidneys were considerably larger than normal. The adrenals were not remarkable. An accessory spleen, 1 cm. in diameter was present. No growth was obtained from cultures of the heart's blood and spinal fluid.

Pathological diagnosis:

1. Acute tracheitis
2. Interstitial pneumonia
3. Focal myocarditis
4. Subacute hepatitis
5. Acute proliferative glomerulonephritis
6. Lymphadenitis
7. Petechial hemorrhages
8. Status post-operative splenectomy, February 2, 1952
9. Accessory spleen

Discussion: The numerous investigations regarding the role of the spleen in natural resistance to infection have resulted in an enormous amount of literature. This work has been compiled, summarized, and reviewed by Perla and Marmorston [3]. A close relationship between a normal functioning of the spleen and the adequate formation of antibodies (i.e., modified gammaglobulins) both quantitatively and qualitatively is believed to exist.

The reporting of clinical experiences similar to the cases reported here may throw light on the relationship between age, function of the spleen, and susceptibility to infection.

Summary: Repeated severe infections ultimately led to death in two brothers whose spleens were removed for idiopathic thrombocytopenic purpura.

Acknowledgments: Dr. C. Francis Scalessa for permission to report these cases, Dr. E. Clarence Rice for the help given in the preparation of this paper, and Colonel Ogden Bruton, M.D., U. S. Army, for his assistance in the determination of the blood proteins.

BIBLIOGRAPHY

1. King, H. and Shumacker, H. B.: Susceptibility to infections after splenectomy performed in infancy. Ann. Surg. **136**: 239, 1952.
2. Gellis, S. S.: Yearbook of Pediatrics, 1953–1954 series, page 88.
3. Perla, D. and Marmorston, J.: Natural resistance and clinical medicine. Boston, Little, Brown and Co., 1941.

CLINICAL PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D., assisted by Grace H. Guin, M.D., and Enid F. Gilbert, M.D.

Discussion by: Ralph D. Whitley, M.D.

PROTOCOL

This 5 year old colored boy was admitted to Children's Hospital with the chief complaints of abdominal pain and fever of 10 days duration. Ten days prior to admission the patient began to experience intermittent colicky abdominal pain lasting two or three minutes and being more severe after a meal. Three days prior to admission he became anoretic. He vomited once seven days prior to admission but not subsequently. There had been no diarrhea or constipation. The temperature had been moderately elevated for ten days prior to admission. No blood or mucus had been noticed in the stools. There had been no weight loss. There had been no known previous illness.

Family history was non-contributory.

Physical examination revealed a well developed and well nourished male. The temperature was 103°, pulse 140 per minute, respirations 22 per minute, and weight 43 pounds. The skin was moderately dry. The ears, nose and throat were normal. The neck was supple. The chest was clear to percussion and auscultation. There was no cardiac enlargement and no heart murmurs were heard. The child held both legs in flexion. The entire abdomen was very tender to palpation. There was muscular rigidity throughout the lower quadrant of the abdomen. Rectal examination was negative.

Laboratory data included: hemoglobin 3.9 gm. per 100 ml., WBC 15,400 with segmented forms 83, bands 8, myelocytes 1, lymphocytes 6, monocytes 1 and eosinophils 1 per cent. Platelets were adequate. No sickle cells were seen. Urinalysis showed: color straw, reaction acid, specific gravity 1.035, albumin and sugar negative, acetone 4 plus. No red or white cells were seen in sediment. X-ray examination of the abdomen in the upright and lateral positions revealed a ground glass appearance over the entire abdomen which was thought to represent a small amount of fluid. There was no evidence of intestinal obstruction. The liver and spleen were not enlarged.

Fourteen hours after admission a laparotomy was performed. On entering the abdominal cavity there was a slight amount of blood-tinged fluid. A mass was palpable measuring 12 cm. x 10 cm. x 5 cm. in the lower pelvis. There was no evidence of small bowel obstruction. The child's postoperative course was unremarkable and he was discharged after ten days.

The child's second admission was six weeks later. Shortly after the first discharge a mass appeared in the right scrotum. This had gradually increased in size. Bowel movements had been consistently normal. There had been no vomiting and there had been no loss of weight. Physical examination now showed that he was still well nourished, but that there was protrusion of the abdomen. Cervical, axillary, and inguinal nodes were unremarkable. Chest was clear to percussion and auscultation. The liver, spleen, and kidneys were not palpable. There was an irregular 4 cm. mass extending down the right side of the abdomen, and a firmer mass on the right side of the abdomen just to the left of the right rectus incision. This mass extended through the inguinal ring, into the scrotum. No fluid wave could be elicited. The masses in the abdomen were tender. The left testis was normal. The right testis could not be palpated since the right side of the scrotum was occupied by a hard mass. There was also a 4 cm. translucent cystic mass in the scrotum. Urinalysis on this admission gave normal findings. The peripheral blood hemoglobin 10 gms., WBC 5,900 with differential of segmented forms 63, bands 3, lymphocytes 27, monocytes 5, eosinophils 1, atypical lymphocytes 1 per cent. The child was discharged 2 days later without any specific therapy. He continued to do poorly at home and finally died three weeks later.

DISCUSSION

Dr. Ralph D. Whitley:

In considering a diagnostic problem such as that presented today, I like to think of myself as playing a game of solitaire and place each card so that in the end the chances are very good I will come up with a winning hand. To accomplish this the cards must first be stacked in orderly piles consisting of the facts presented in the protocol. The first pile should contain those cards localizing the site of pathology within the body. The first card in this pile should be the chief complaint of abdominal pain, localizing a major symptom to the abdomen. Fever is a generalized response and this card should be placed on a discard pile to be played later where it will produce the most telling effect. A history of vomiting and anorexia would point to gastro-intestinal disturbance, and point to the abdomen as the site of pathology. The fact that the whole abdomen was tender to palpation and that there was muscle rigidity throughout the lower quadrants of the abdomen would pinpoint the localization of the pathology to the abdomen and complete the first pile of cards.

The next step is to localize the pathology within the abdomen and consider what organs might be involved; this would constitute the second pile of cards. The fact that the entire abdomen was tender would incriminate this segment of the body with its contents. On reading further, we learn that there was muscular rigidity throughout the lower quadrants, and the child held both legs in flexion. This would localize the disease to the lower abdomen; this is further confirmed by the fact that a mass measuring 12 cm. x 10 cm. x 5 cm. was found in the "lower pelvis" on laparotomy 14 hours after admission; thus, our second stack of cards is completed.

Our third stack of cards in this game of pathological solitaire is a listing of all the tissues and structures found in this area, and discarding those which according to the facts presented are obviously not involved. These might be listed as: 1. skin; 2. subcutaneous tissue; 3. fascia; 4. muscles; 5. blood; 6. bone; 7. small intestine; 8. large intestine; 9. kidneys; 10. scrotum and its contents; 11. bladder and prostate; 12. nervous tissue; 13. lymph nodes. From the case history I feel that the first six items can be eliminated and will not be considered further.

At this point, we form a fourth stack of cards, and come back to stack number three a little later; connecting stacks three and four in the final analysis so that we may come up with the winning card—the diagnosis. In this stack is the type of pathology; this again may be arrived at by a process of elimination. If we roughly classify pathology into the following categories: 1. congenital anomalies; 2. infections; 3. trauma; 4. metabolic disorders; 5. neoplasm (benign or malignant), we quickly arrive at category number five (neoplasm) since we are told that at operation a tumor measuring 12 cm. x 10 cm. x 5 cm. was found in the lower pelvis. So far our game has been elementary; now comes the difficult part of playing with the cards in stacks 3 and 4 to determine the type and site of neoplasm.

To move a little closer to our final card, I feel we can safely consider the neoplasm as malignant, viewing the rapid downhill course in an otherwise healthy five-year-old child. The fact that the bloody fluid was found in the abdomen at operation would tend to confirm the malignancy of the lesion.

To reduce stack number three, I feel we can rule out the gastro-intestinal tract as the source of the tumor, since the only finding pointing to the gastro-intestinal tract was the colicky pain, anorexia with transient vomiting. This possibility was dispelled at operation.

It is now time to explore our fifth and last pile of cards. The most likely malignant neoplasm involving the kidneys, scrotum and contents, bladder and prostate, lymph nodes, and nervous tissue would be: 1. embryoma of the kidney (Wilms' tumor); 2. hypernephroma of the kidney (Grawitz); 3. primary tumors of prostate and bladder; 4. primary tumors of testicles; 5. ganglioneuroma; 6. liposarcoma; 7. neuroblastoma; 8. lymphoma, a. Hodgkin's disease, b. lymphosarcoma.

The first three conditions, embryoma of kidney, hypernephroma of kidney, and Wilms' tumor, will only be considered briefly since it is very unlikely that anyone of these would produce a mass such as described lying in the "lower pelvis".

Embryoma of the kidney (Wilms' tumor) is the most common tumor of the abdomen in childhood. Metastases occur through the retroperitoneal lymphatics, and by invasion of the blood stream through the renal veins. However, Wilms' tumor has a tendency to reach a large size before

metastases occur. Metastases are particularly prone to develop in the lungs before involvement in other organs or in the skeleton. The mass is characteristically quite painless until it reaches enormous proportions, and even then seldom produces more than a dull ache or discomfort. Urinary complaints are quite rare, but low-grade fever, explained on the basis of hemorrhage, is common.

This is more frequent between the ages of two and three years and must be differentiated from neuroblastoma sympatheticum, which is not apt to be so large as an embryoma, and metastasizes early to the liver and particularly to the skeleton. Lungs are only involved late in the disease. Neuroblastomas are firm and hard with a finely nodular surface.

Hypernephroma (Grawitz tumor) of the kidney is exceedingly rare in childhood and need not be considered in this discussion.

Primary tumors of the prostate and bladder are rare in children, there being an approximate incidence of one bladder tumor in a child to each 950 bladder tumors in adults. Practically all are sarcomas. Since these growths originate from sub-epithelial structures, they develop without giving rise to clear-cut symptoms, such as initial hematuria as seen in adults. In this case, there was no evidence of bladder involvement, even on the second admission and I feel this organ can be eliminated on a primary site.

The possibility of a primary tumor of the testicle is very remote as no enlargement or tumor mass was noted in the testicle on first admission, and the mass described on the second admission was undoubtedly either due to metastasis or direct extension of the abdominal tumor.

Ganglioneuromas originate from the anlage of the sympathetic nervous system which go to form the adrenal medulla. These tumors are well encapsulated, grow slowly, are composed of a mixture of ganglion cells, and are benign. This is not true of the tumor under discussion.

Liposarcomas may arise in the retroperitoneal region, particularly in the true pelvis. These tumor are rare in children, and do not tend to be so rapidly fatal as the case presented here.

This narrows the field to two possibilities: 1. neuroblastoma; 2. lymphoma, including Hodgkin's disease and lymphosarcoma. Both of these are possibilities.

Except for leukemia, neuroblastoma is the most frequently encountered malignant neoplasm of infancy and childhood. When it occurs in the abdomen it is about half as common as the embryoma of the kidney. It is most commonly derived from the adrenal medulla, but may arise from sympathetic tissue anywhere in the body. It tends to metastasize early and widely. The tumors grow with considerable rapidity but may remain encapsulated for a short period before they spread along tissue planes, invade surrounding organs, and metastasize by way of lymphatics, and especially the blood stream. About 80 percent of neuroblastomas occur in

the first five years of life and the swelling is generally painless. The history in most cases includes increasing fatigue and weight loss for several months. Loss of appetite is common.

This brings us down to the last and most likely diagnosis in the case presented: a lymphoma, either Hodgkin's disease or lymphosarcoma.

Hodgkin's disease generally makes its appearance in the cervical region, but any group of nodes may be involved. Mesenteric nodes sometimes form astonishingly large swellings in the abdomen. Secondary enlargement of the spleen occurs in about 60 percent of cases. Pruritis which sometimes appears early is often persistent and severe. Fever is frequent and significant, and where abdominal fluid is present this may be bloody. Anemia is rarely present in the early stages, but is distinctive as the disease progresses. In the acute form death occurs within a few weeks or at most months. In the abdominal form the disease tends to involve the deep nodes and some superficial nodes may escape.

Lymphosarcoma is likely to be more rapid in its course and is more frequently seen in children than Hodgkin's disease. Since we are now down to our last card, lymphoma, I believe that this is the correct diagnosis, the involvement of the retroperitoneal lymph nodes making the more specific diagnosis of lymphosarcoma possible.

Dr. E. Clarence Rice:

In a child five years of age the most common abdominal tumors which we see are embryoma of the kidney (Wilms' tumor), neuroblastoma and the lymphomas. In those children under three years of age, the embryonic tumors of the kidney and the sympathetic nervous system are more frequently seen. Occasionally a walled-off appendiceal abscess may confuse the diagnosis. In the younger children the rapid growth of the malignant tumor is such that emaciation is not frequently seen at the time of initial admission to the hospital. Fever and moderate leukocytosis may be present. In the patient with an abdominal tumor and absence of apparent involvement of the kidneys, long bones and orbital pathology, the diagnosis of the embryonic tumors mentioned above would tend to be ruled out. At the age of this child and beyond, the lymphomas are met with increasing frequency. Carcinomas are infrequently seen.

Of the malignant tumors of the lymphoma group, lymphosarcoma is the commonest, followed by Hodgkin's disease. Reticulum cell sarcoma is rarely seen in children and we have rarely encountered giant follicular lymphadenopathy in juveniles under twelve years of age.

Practically all of the patients that we have seen with Hodgkin's disease have had involvement of the cervical lymph nodes and the disease tends to advance at a slower rate than lymphosarcoma.

Symmers lists five different groups of lymphosarcoma and states that

the group that involves the lymphoid tissues of the abdomen is the most common. In the abdominal type generalized lymph node involvement may not be evident early to the clinician, making the diagnosis difficult, especially if there is sufficient involvement of the bowel to cause obstruction. Perforation and obstruction of the bowel are reported with sufficient frequency as to make one think of this type of malignant tumor when either of these happenings mentioned above occurs or is suspected. Leukosarcoma may be a terminal event.

The diagnosis of the exact type of lymphoma that the physician is dealing with can only be made with certainty by the microscopic examination of the biopsied tissue.

Irradiation, steroids and chemotherapy usually give initial symptomatic relief, but their value is of relatively short duration.

PATHOLOGY REPORT

Enid F. Gilbert, M.D.:

Unfortunately, this patient died at home, and we were unable to perform an autopsy.

At operation, a mass measuring 12 cm. x 10 cm. x 5 cm. was palpated in the pelvis. On delivery of this mass into the operative site it was found to be a tumor involving the small bowel, which had perforated. There were two large masses in the mesentery of the small bowel, both measuring approximately 5–6 cm. in diameter. The aortic chain, as well as numerous mesenteric lymph nodes, were involved in the tumor mass. There was no evidence of small or large bowel obstruction. The portion of ileum which contained the perforated area was resected.

The specimen which was removed at operation was submitted for pathological examination. It consisted of a globular tumor mass measuring 12 cm. x 8 cm. x 5.5 cm., and it weighed 260 grams.

The tumor had been opened on one side, exposing a circular interior measuring 4 cm. x 8 cm. The exterior of the mass was grayish pink and friable, and its wall measured 3 cm. in thickness. On the wall opposite the opened portion was a perforation measuring 2 cm. in diameter. The tissue in that portion of the mass was necrotic.

The report on microscopic examination was lymphosarcoma.

Final diagnosis

Lymphosarcoma of ileum with metatastic invasion of mesenteric, aortic and inguinal lymph nodes.

EDITORIAL

SPLENECTOMY AND INFECTION

Once again, with the questions raised by Hoefnagel's article elsewhere in this issue, the spleen is introduced as an organ of mystery.

The death of two children due to overwhelming infection following splenectomy poses the hypothesis that the spleen is vitally responsible for certain defense mechanisms and that, at least in infants and children, absence or removal of the spleen may cause increased susceptibility to serious infections. The hypothesis is supported partially or fully in published or verbal comments by Rice [1], King and Shumacker [2], Gellis [3], Smith [4], and Ivemark [5]. The latter author uncovered 11 instances of severe infection among 66 cases of asplenia. Thus far no one has presented conclusive supporting evidence. Among those questioning the validity of the hypothesis are Gross, according to Gellis [6], and Howell according to Ivemark [5]. Howell mentions, however, the occurrence of 2 cases of meningitis among 18 infants undergoing splenectomy, an incidence probably greater than average for infants.

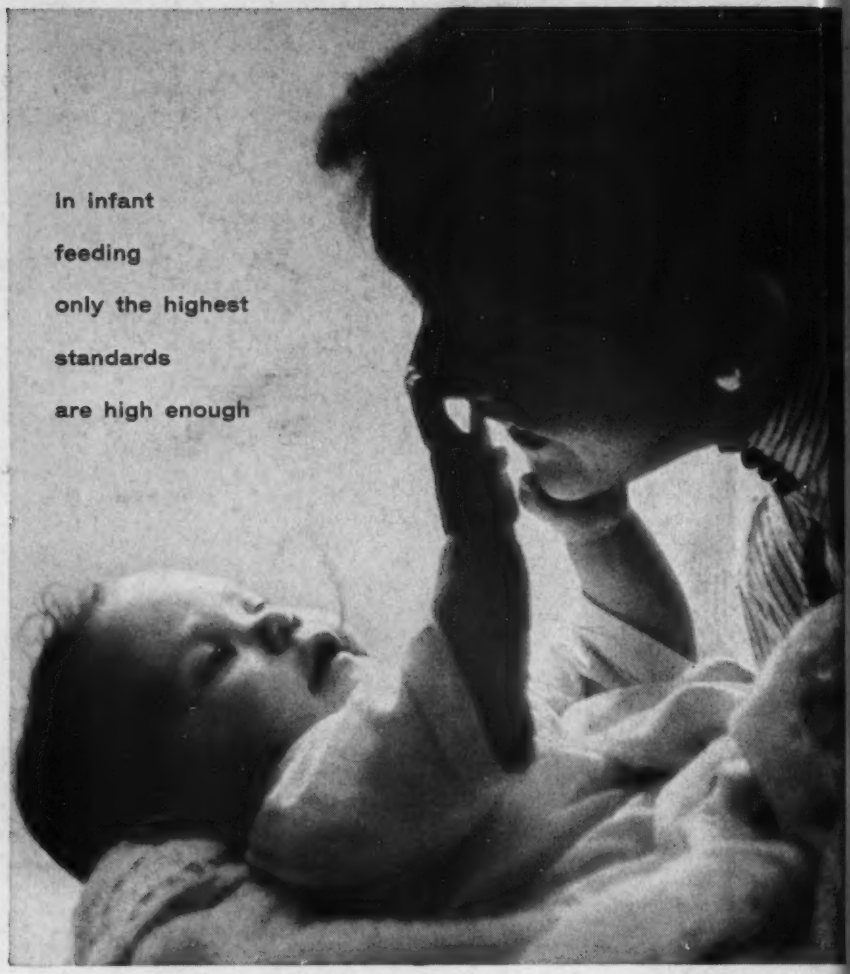
There are of course several alternate explanations for the reported cases of apparently increased susceptibility to infection following splenectomy. The infections may be coincidental, and can be explained as well by the underlying reason for splenectomy or the general poor state of health of patients undergoing splenectomy. Insufficient control observations have been made of relative incidence of infection in patients of similar age groups who 1) have the same underlying disease but have not had splenectomy or who have undergone similarly extensive surgery but not splenectomy; or 2) have had splenectomy for reasons such as trauma wherein systemic disease is not a problem.

Apart from the clinical observations, there is much controversy in theory about the physiology of the spleen and its role in resistance. It is certainly not the only organ of resistance but most investigations confirm that it has the capacity for participating in the defense functions of the reticuloendothelial system (phagocytosis) and the lymphatic system ("filtration", lymphocytic inflammatory response). The red pulp contains plasma cells (antibody globulin production) and "The concensus of conclusions . . . . points to this organ, in the mammal at least, as an important depot for the formation of antibodies" [7]. In theory then, it might be that these splenic functions of defense are called upon only when stress is severe and the body's other depots are working at capacity. Nonetheless, the hypothesis that splenectomy in the infant or child increases susceptibility to infection remains unproven. There is enough suggestion in theory and in the presently

reported cases however, to warrant: 1) Further control studies such as those mentioned above; 2) More careful consideration of indications for splenectomy especially in infants and children; 3) More careful supervision of the postoperative course of the child whose spleen has been removed.

REFERENCES

1. Rice, E. C., Personal Comment.
2. King, H., Schumacker, H. B., Splenic Studies: 1. Susceptibility To Infection After Splenectomy Performed In Infancy. Ann. Surgery **136**: 239–242, 1952.
3. Gellis, S. S., Footnote To Abstract Of Paper By Boggs And Reed. Yearbook Of Pediatrics, p275, 1954–1955.
4. Smith, Carl H., Communication to E. C. Rice.
5. Ivemark, B. I., Implications Of Agenesis Of The Spleen On The Pathogenesis Of Cono-Truncus Anomalies In Childhood. Acta Paediat. **44**: Suppl. 104, 65–67, 1955.
6. Gellis, S. S., Footnote To Abstract Of Paper By King And Schumacker. Yearbook Of Pediatrics, p89, 1953–54.
7. Raffel, S., Immunology, Hypersensitivity, Serology, N. Y., Appleton Century Crofts, 1953.



For 45 years **Dextri-Maltose®**—

Mead carbohydrate manufactured specifically for infant formulas—has been prepared with meticulous care to meet the highest standards of nutritional and pharmaceutical excellence.

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

MEAD, JOHNSON & COMPANY, Suite 419 Eig Building, 8641 Colesville Road,
Silver Spring, Maryland. JUniper 9-1222